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Food and Drug Administration
Rockville MD 20857

DEC 21 2001

WARNING LETTER
Via Federal Express

Mark H. Feldman, DPM
15700 N.W. 67 Avenue
Miami Lakes, Florida 33014

Dear Dr. Feldman:

The purpose of this Warning Letter is to inform you of objectionable conditions found during a Food and Drug Administration (FDA) inspection conducted at your clinical site, to discuss your written response to the deviations noted, and to request a prompt reply with regard to the remaining issues. The inspection took place during the period of August 20 through September 24, 2001, and was conducted by Mr. Victor Spanioli, an investigator from FDA's Florida District Office. The purpose of the inspection was to determine if your activities as a clinical investigator in [REDACTED] study of the [REDACTED] comply with applicable FDA regulations. This [REDACTED] is a device as that term is defined in Section 201(h) of the Federal Food, Drug, and Cosmetic Act (the Act).

The inspection was conducted under a program designed to ensure that data and information contained in requests for Investigational Device Exemptions (IDE), Premarket Approval Application (PMA), and Premarket Notification [510(k)] submissions are scientifically valid and accurate. Another objective of the program is to ensure that human subjects are protected from undue hazard or risk during the course of scientific investigations.

Our review of the inspection report submitted by the district office revealed serious violations of requirements of Title 21, Code of Federal Regulations (21 CFR), Part 812 - Investigational Device Exemptions, Part 50 - Protection of Human Subjects, and Section 520(g) of the Act. You received a Form FDA 483, "Inspectional Observations," at the conclusion of the inspection that listed the deviations noted and discussed with you. We acknowledge receipt of a copy of your response to Mr. Spanioli dated November 7, 2001. The deviations noted on the Form FDA 483, our subsequent review of the inspection report, and your response to the Form FDA 483 items are discussed below. The deviations noted include:

Failure to obtain signed and dated study informed consent documents from all study subjects. (21 CFR 812.100, 50.20, and 50.27)

Several study subjects had not signed the study informed consent document at the time of the inspection. As stated in 21 CFR 812.100, an investigator is responsible for ensuring that informed consent is obtained in accordance with 21 CFR Part 50.

According to 21 CFR 50.20, no investigator may involve a human being in an investigational study unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative. Moreover, 21 CFR 50.27 requires that informed consent is documented by the use of a written consent form approved by the institutional review board (IRB) and signed and dated by the subject or the subject's legally authorized representative.

In addition, you failed to provide study subjects with a copy of their signed informed consent document. 21 CFR 50.27 requires that a copy of the signed and dated informed consent document be given to the person signing the form. At the time of the inspection, no study subject had been provided a copy of the signed informed consent document.

Failure to maintain device accountability records. (21 CFR 812.140(a)(2))

Records available at [REDACTED], where the inventory of investigational [REDACTED] was maintained, consisted of purchasing records only. As stated in 21 CFR 812.140(a)(3), a participating investigator is required to maintain accurate, complete, and current records of the receipt and use or disposition of all investigational devices. This includes: records of the type and quantity of the device, the dates of receipt, and the batch numbers or code marks; the names of all persons who received, used, or disposed of each device; and information regarding why and how many units of the device have been returned to the sponsor, repaired, or otherwise disposed of.

Failure to conduct the study in accordance with the investigational plan. (21 CFR 812.100 and 812.110)

Numerous protocol violations were noted. These include: failure to perform all required tests at all study visits; failure to return [REDACTED] devices to the sponsor; performance of auxiliary surgery during [REDACTED] of the investigational device; and failure to maintain copies of case report forms (CRFs) submitted to the sponsor.

Failure to maintain accurate, complete, and current subject records. (21 CFR 812.140(a)(3))

Copies of CRFs retrieved from the sponsor revealed that some study subjects lacked CRFs and that many CRFs were incomplete. Many CRFs were completed months after subject visits. In addition, not all information recorded on the CRFs could be documented in subject source records.

Failure to submit progress reports to the sponsor and reviewing IRB. (21 CFR 812.150(a)(3))

Study progress reports were not submitted to the sponsor or to one of the two reviewing IRBs. An investigator is required to submit progress reports on the

investigation to the sponsor and the reviewing IRB(s) at regular intervals, but in no event less often than yearly.

In addition to the deviations listed above, you failed to submit protocol changes to the reviewing IRBs for review and approval and did not have IRB review of your subject recruitment materials or materials included on your web site regarding this [REDACTED]. An advertisement used to recruit study subjects did not disclose the fact that the [REDACTED] was investigational. FDA considers all materials available to subjects and potential subjects of a clinical trial as educational materials and, therefore, part of the informed consent process. As such, these materials must be reviewed and approved by the reviewing IRB(s) prior to use.

The deviations listed above are not intended to be an all-inclusive list of deficiencies that may exist in your clinical study. It is your responsibility as a clinical investigator to ensure that an investigation is conducted according to the signed agreement, the investigational plan, and applicable FDA regulations.

Your November 7 response addresses each of the Form FDA 483 items. You state that a number of the informed consents that were listed as missing were actually held at the sponsor site. These documents should be retained in the subject files at your site, as 21 CFR 812.140(a)(3) requires an investigator to maintain accurate, complete, and current records of each subject's case history and exposure to the device, including signed and dated consent forms. You further state that all subjects signed hospital consents pertaining to the operation and were verbally informed prior to surgery. As stated in 21 CFR 50.20, an investigator is required to seek consent under circumstances that provide the prospective subject or the subject's representative sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence. Moreover, as stated above, regulations require that a written informed consent document be signed and dated by the subject or the subject's legal representative and that the subject receive a copy of the signed document. It is the responsibility of the clinical investigator to assure that this occurs for all study subjects. Please assure that all study subjects have signed and dated a study informed consent as soon as possible. Please provide us, at the address given below, copies of informed consent documents for all subjects listed in item one of the Form FDA 483 (copy enclosed).

Your response states that the protocol does not require that a copy of the signed and dated informed consent document be provided to the study subject. As stated in the previous paragraph, this is a regulatory requirement. (See 21 CFR 50.27.) According to 21 CFR 812.100 and 812.110, it is the responsibility of the clinical investigator to adhere to all applicable FDA regulations. Please provide all study subjects a copy of their signed and dated informed consent document as soon as possible.

You state that the informed consent document was approved by FDA as it stands. In reviewing an IDE submission, FDA reviews the informed consent document proposed by the sponsor to assure that the required elements are included; however, no actual approval is given. The basic elements, which are listed in 21 CFR 50.25, include a description of any reasonably foreseeable risks or discomforts. The intent of the regulation with regard to this element is that subjects are made aware of all pertinent information available at the time of their participation. Therefore, it is expected that this be updated if information from the study reveals additional information in this regard.

Regarding the [REDACTED] FDA does not agree that the [REDACTED] supplied as [REDACTED] meet the definition for a custom device. (The definition for custom device is found at 520(b) of the Act and also at 21 CFR 812.3(b).) Since the [REDACTED] is an investigational device that is the subject of a clinical trial, use of a modified [REDACTED] by a clinical investigator is a protocol deviation. Such protocol deviations need to be reported to the reviewing IRB(s) and included on the subject's CRF.

With respect to progress reports due to the IRB at [REDACTED], you state that you will update them regarding the three study subjects treated there. Please submit this report to them as soon as possible and please send us a copy of the report and any accompanying cover letter at the address listed below.

Your response states that the [REDACTED] that resulted in [REDACTED] is not an adverse device effect and that there were no unanticipated adverse device effects in any of your study subjects. The possibility of this [REDACTED] with the possible requirement of additional procedures, was not included in either the study protocol or the informed consent document and therefore is correctly considered an unanticipated adverse effect for this study. Moreover, any occurrence, whether anticipated or unanticipated, that differs from a routine recovery from the procedure and the ability of the [REDACTED] to function as intended must be recorded and reported to sponsor for inclusion in progress reports to the FDA. This allows both the sponsor and FDA to review the number and severity of such events that occur across the study. From this review a determination can be made if the investigational device and/or the required accompanying procedures result in adverse effects unexpected for the category of device or, for commonly occurring effects, if they occur more frequently than would be anticipated.

With regard to the observations that information on CRFs was incomplete, incorrect, or unsubstantiated by source documents, you state that [REDACTED] has performed an extensive site visit to correct and clarify discrepancies in the CRFs. You state that both you and [REDACTED] are now confident of the accuracy and reliability of the forms and will submit them for review if requested. This response does not address the specific items included under this observation on the Form FDA 483. For example, it was noted that the [REDACTED] for two subjects were altered such that the

resulting values would qualify them for the study while the original scores would not. Moreover, many of the forms were completed months after the visit for which information was recorded, source documents did not contain information relevant to all areas completed, and there was no documentation as to the source of such information. Review of the forms as completed with the [REDACTED] representative would not address these issues. Please respond separately to each of the findings listed under this observation (number 10) on the Form FDA 483.

In a related issue, you state that documentation of post-operative rehabilitation and follow-up surgeons' notes have been obtained for all study participants and are now part of your records. Many of the study subjects treated at your site were not local and post-operative treatment was the responsibility of their individual physicians and/or rehabilitation personnel in their home area. At the time of the inspection there was no indication that any of these medical personnel were officially part of the study or that they had been aware of the study requirements. Please explain and document how you were able to obtain all of the pertinent information to accurately complete the CRFs for follow-up visits for these study subjects.

Regarding the observation that you performed auxiliary corrective surgery not indicated in the study protocol, you state that such surgery was not contra-indicated. The type of surgery listed in the inspectional report includes [REDACTED] and [REDACTED]. Such procedures directly affect the success or failure of the investigational device. Moreover, any procedure performed during the use of an investigational product, whether it directly affects the device or not, needs to be included on the CRF. In addition, for the results of a clinical study to support a submission for marketing, all clinical investigators need to strictly follow the protocol. If the subjects for whom you performed auxiliary surgery required additional surgical repair to permit use of the [REDACTED], they were not appropriate candidates for the study and their inclusion represents a protocol deviation. Such deviations decrease the number of subjects whose results can be combined in support of the safety and effectiveness of the device and could therefore jeopardize the usefulness of the clinical trial. It is essential that all study subjects meet the requirements of the inclusion/exclusion criteria and that, with the exception of medical emergencies, procedures and/or treatments not specified in the protocol are avoided.

Your response states that device accountability records are kept at [REDACTED] [REDACTED] that you do not have access to or control of these records, and that the protocol does not require you to perform this hospital function. [REDACTED] maintained the inventory of investigational devices needed for the study and therefore retained appropriate records of receipt and payment. However, as stated above, 21 CFR 812.140(a)(2) requires a clinical investigator to maintain accurate, complete, and current records of the receipt and use or disposition of investigational devices. Moreover, it is your responsibility according to 21 CFR 812.110(c) to assure that only authorized personnel have access to these devices.

You state that there was no requirement in the protocol to document that study subjects had not responded to non-operative treatment for a period of six (6) months. Lack of response to non-operative treatment over this time period is the sixth of eleven (11) inclusion criteria listed in the investigational plan. Documentation that subjects included in the study meet the study inclusion/exclusion criteria is expected.

With regard to advertisements regarding the investigational [REDACTED], you state that all future advertisements will include the fact that it is investigational and that your press releases did include this statement. Such a disclaimer is not sufficient to address our concerns regarding advertisement for an investigational device. Enclosed is a copy of the FDA guidance regarding information that can be made available concerning investigational products, *Preparing Notices of Availability of Investigational Medical Devices and for Recruiting Study Subjects*. Moreover, your web site is of concern to us, as it commercializes an investigational product and makes statements regarding the safety and effectiveness of the device for the purposes for which it is being studied.

In response to a number of the Form FDA 483 statements you state that an observation is correct but give no corrective action to remedy it or prevent its reoccurrence. For example, the fact that protocol changes were not submitted for IRB review and approval and that periodic progress reports were not submitted to the sponsor. These are regulatory requirements. Your response in general indicates a continued lack of understanding of the regulatory requirements clinical investigators must meet, and your response includes few corrective actions taken or planned with regard to the deviations noted during the inspection. The inspectional report notes that Mr. Spanioli provided you with a copy of 21 CFR Parts 50, 54, 56 and 812. Part 812 describes your responsibilities as a clinical investigator of an investigational medical device and Part 50 includes what is required to protect the welfare of study subjects. Part 54, Financial Disclosure by Clinical Investigators, includes information regarding your regulatory responsibilities with regard to any financial interest you might have in the outcome of studies in which you participate. Part 56, Institutional Review Boards, covers the responsibilities of IRBs and what an IRB expects from you as a clinical investigator, as well as their responsibilities to you.

In addition to responding to the specific requests listed above, please inform us of the corrective actions you have taken or plan to take with regard to the deviations noted. Please send all requested information, within 15 working days of receipt of this letter, to the Food and Drug Administration, Center for Devices and Radiological Health, Office of Compliance, Division of Bioresearch Monitoring, Program Enforcement Branch II (HFZ-312), 2098 Gaither Road, Rockville, Maryland 20850, Attention: Jean Toth-Allen, Ph.D. Failure to respond could result in regulatory action without further notice, including initiation of investigator disqualification procedures.

A copy of this letter has been sent to FDA's Florida District Office, 555 Winderley Place, Suite 200, Maitland, Florida 32751. We request that a copy of your response also be sent to that office.

If you have any questions, feel free to contact Jean Toth-Allen, Ph.D. at (301) 594-4723, ext. 141.

Sincerely yours,

Charlene Allen, RPh, RAC

for

Larry Spears
Acting Director
Office of Compliance
Center for Devices and Radiological
Health

Enclosures

cc:

[REDACTED]